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Importance of chemical pretreatment for bioconversion of lignocellulosic biomass

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A B S T R A C T

Lignocelluloses are often a major or sometimes the sole components in different waste streams from various sources such as industries, forestry, agriculture and municipalities. It represents an as-of-yet untapped source of fermentable sugars for significant industrial use. Many physico-chemical, structural and compositional factors hinder the hydrolysis of components present in the biomass to sugars and other organic compounds that can later be converted into fuels. During the past few years, a large number of chemical pretreatment methods including lime, acid, steam explosion, sulfur dioxide explosion, ammonia fiber explosion, ionic liquid and others have been developed for efficient pretreatment of biomass. Many pretreatment methods have shown high sugar yields i.e. more than 90% of the theoretical yield from lignocelluloses. In this review, we discuss various chemical pretreatment processes, feasibility of the processes at industrial scale in terms of the mechanisms involved, advantages, disadvantages and economic assessment. It is not possible to define the best pretreatment method as it depends on many factors such as type of lignocellulosic biomass, process parameters, environmental impact, economical feasibility, etc. However, some of these chemical pretreatments have disadvantages such as formation of inhibitory compounds especially furfural and 5-hydroxyl methyl furfural (HMF).

Contents

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1. Introduction

The depletion of fossil fuel reserves, the unstable panorama of the fuel prices and, more recently, increasing environmental and political pressures have increased the industrial focus towards alternative fuel resources, and encouraged the search of plant biomass derived fuels [1,2]. Biomass is inexpensive, renewable, widely available and environment friendly. Extensive research has been carried out on ethanol production from lignocellulosics in the past two decades [3–5]. The advances in microbiology, biotechnology and genetic engineering are leading to a new concept for converting renewable biomass to valuable products. The integration of these biomass-based processes into the commercialization will provide the possibility for the development of sustainable model for the production of commodity products [6]. In this respect, lignocellulosic biomass has contributed towards an alternative to the petroleum-based transportation fuel [7].

Lignocellulosic wastes (LCW) are composed of cellulose, hemicellulose and lignin [8]. Some other materials such as ash, proteins, pectin, etc. are also found in the lignocellulosic residues in different proportion based on the sources [9]. These may be categorized based on their sources such as industrial waste (sawdust, paper mill discards, food industry residues, etc.), forestry waste (grasses, hard and soft wood, etc.), agricultural residues (straws, stovers, peelings, cobs, stalks, nutshells, non-food seeds, etc.), domestic wastes (kitchen wastes, sewage, waste papers, etc.), and municipal solid wastes [10,11]. Due to the close association of cellulose and hemicellulose with lignin in the plant cell wall, pretreatment is necessary to make these carbohydrates available for enzymatic hydrolysis and fermentation [12].

Pretreatment can partially remove lignin and hemicellulose, reduce cellulose crystallinity, and increase the porosity (accessible surface area) of the biomass [13,14]. Various physical, chemical and biological pretreatment methods have been investigated by various researchers in the last three decades. Among all the investigated pretreatment methods, chemical pretreatment has been proven to be a promising one when these were followed after anaerobic digestion [15]. During the process of chemical pretreatment, degradability remains mainly in the solid phase, and the subsequent solid separation is easy. However, a large amount of chemicals and water are required in most of the chemical pretreatments, which need recycling of chemicals, disposal of waste solution, and sometimes high temperature and thus, could result in high facility investment, high treatment cost and potential environmental pollution [16,17]. Although, a large portion of glucose and xylose are degraded to hydroxymethyl furfural (HMF) and furfural, respectively, which are found to be inhibitory to microbial processes [4,18]. This review is based on various chemical pretreatment processes, their industrial applications in terms of the mechanisms involved, advantages, disadvantages and economic feasibility.

2. Necessity of pretreatment

The pretreatment process is required to break down the lignin structure and disrupt the crystalline structure of cellulose, so that the acids or enzymes can easily access the cellulose to hydrolyze into monomers [16,17]. Pretreatment allows to change the structure of the lignocelluloses such as increasing the surface area and porosity of biomass; modifying and removing the lignin, partially polymerizes and removes the hemicelluloses, and reduces the crystallinity of cellulose [19]. The pretreatment processes solely or in combination can enhance the bio-digestibility of the wastes for biofuel production, and increase accessibility to the enzymes [20,21]. It results in increase in digestibility of the difficult biodegradable materials, and improves the yield of ethanol or biogas from the wastes (Fig. 1).

Although the pretreatment is a most expensive process in biomass-to-fuels conversion, it has a great potential for improvement in the efficiency of the process and lowering of the cost through further investigations [22,23]. Recent investigations have clearly proven that there is a direct correlation between the removal of lignin and hemicelluloses and the digestibility of cellulose [24,13]. Theoretically, fractionation of any biomass species allows to solubilize the majority of the hemicelluloses into the solution, and leaves the cellulose fraction intact [25,26].

3. Pretreatment processes

Pretreatment methods can be divided into different categories: physical (milling and grinding), physic-chemical (steam explosion, hydrothermolysis, wet oxidation, etc.), chemical (alkali, dilute acid, oxidizing agents and organic solvents), biological, electrical, or a combination of these [13,22,23,27]. The schematic configuration of pretreatment is shown in Fig. 2. The following pretreatment

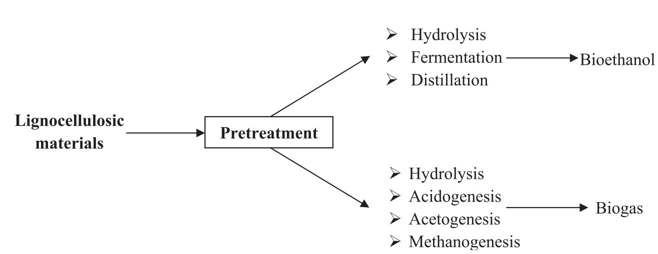


Fig. 1. Pretreatment of lignocellulosic materials prior to bioethanol and biogas production.

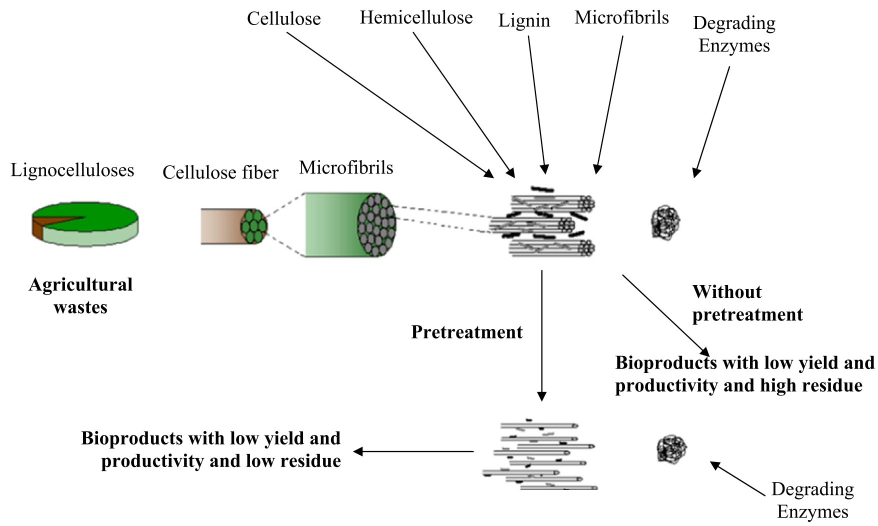


Fig. 2. Schematic diagram of the effect of pretreatment process to lignocellulosic biomass [244].

processes have been investigated for biological conversion of lignocellulosic biomass to fuels and other valuable chemicals.

3.1. Physical pretreatment

Physical pretreatment is used to increase the accessible surface area and pore size of lignocelluloses, and to decrease the crystallinity and degree of polymerization of the cellulose present in lignocelluloses [16]. Different types of physical processes such as milling (ball milling, two-roll milling, hammer milling, colloid milling and vibro energy milling), chipping, grinding and/or irradiation (gamma rays and electron beam) can be used to improve the enzymatic digestibility of lignocellulosic waste materials [28,29]. Size reduction is used in most research studies of hydrolysis, but little information is available about the characteristics of the substrate and energy consumption in the process [30]. Taking into account the high-energy requirement of milling on an industrial scale and rise in the energy demands, it is unlikely that milling is still economically feasible [22].

Size reduction is one of the most effective methods for increasing the enzymatic accessibility to lignocelluloses. However, many of the physical methods for size reduction (milling and grinding) are not economically feasible because of high-energy requirement. In this context, extrusion is a novel and promising physical pretreatment method for biomass conversion to biofuel production. In extrusion, materials are subjected to heat, mix and shear, which result in physical and chemical modifications in the biomass after passing through the extruder. The extruder has many advantages, such as the ability to provide high shear, rapid heat transfer and mixing [31].

3.2. Chemical pretreatment

Chemical pretreatment has become one of the most promising methods to improve the biodegradability of cellulose by removing lignin and/or hemicelluloses, and to decrease the degree of polymerization (DP) and crystallinity of the cellulosic component in lignocelluloses [8,32]. It has been extensively investigated to be used for delignification of cellulosic material in the pulp and paper industry [33]. It has also been exploited to enhance biomass digestibility in an industrial pretreatment process [34]. Further, there are some chemicals, which have been reported to have significant effect on the native structure of lignocellulosic biomass, do not produce toxic residues for the downstream processes, and where the reactions are carried out at room temperature and pressure [8].

Chemicals ranging from oxidizing agents, alkali, acids and salts can be used to degrade lignin, hemicelluloses and cellulose from lignocellulosic wastes. Organic acids such as oxalic acid, acetylsalicylic acid and salicylic acid can also be used as a catalyst, whereas an organic or aqueous organic solvent mixture with inorganic acids (HCl or H_2SO_4) is also used to break the internal lignin and hemicellulose bonds [24,35,36]. However, concentrated acids are not preferred because they are corrosive and must be recovered to make the pretreatment economically feasible [32,37,38].

3.3. Physico-chemical pretreatment

Pretreatments that combine both the chemical and physical processes are of importance in dissolving hemicellulose and alteration of lignin structure, which provides an improved accessibility of the cellulose for hydrolytic enzymes [39,22]. This category includes the vast majority of pretreatment methods such as steam explosion, liquid hot water, ammonia fiber/freeze explosion, wet oxidation, ammonia recycle percolation, aqueous ammonia, organosolv and CO_2 explosion [13,17]. Recently, ionic liquids and cellulose solvent-based lignocellulose fractionation processes have been proposed [40,41]. These types of pretreatments depend on process conditions and solvents used that affect the physical and chemical properties of the biomass.

3.4. Biological pretreatment

Biological pretreatment is mostly associated with the action of fungi that are capable of producing enzymes to degrade lignin, hemicelluloses and polyphenols present in the biomass. It has attracted interest because of its potential advantages over physical/chemical pretreatments such as substrate and reaction specificity, low energy requirements, no generation of toxic compounds, and high yield of desired products [42,43]. However, its disadvantages are as apparent as its advantages, since biological pretreatment is a very slow process and requires careful control of growth conditions and large space to perform [39]. In addition, most lignolytic microorganisms solubilize/consume not only lignin but also hemicellulose and cellulose [44,45]. Therefore, the biological pretreatment faces techno-economic challenges and is found less attractive commercially. Further, pretreatment of biomass is a global issue that demands an environment friendly process. Thus,

Table 1
Effect of different chemical pretreatment on different feed-stocks and yield.

S. no.	Pretreatment method	Feed-stock	Pretreatment conditions	Yield	Refs.
1.	Acid pretreatment	Sugarcane bagasse	2–6% H_2SO_4, 100–128 °C temp, 0–300 min	21.6 g/L xylose, 3 g/L glucose, 0.5 g/L furfural and 3.65 g/L acetic acid in 24 min at 122 °C and 2% H_2SO_4	[227]
2.	Acid pretreatment	Eucalyptus residue	0.65% (w/w) H_2SO_4, 157 °C temp, 20 min	1.65 g/L glucose, 13.65 g/L xylose, 1.55 g/L arabinose, 3.10 g/L acetic acid, 1.23 g/L furfural and 0.20 g/L HMF	[228]
3.	Acid pretreatment	Olive tree pruning	0.75 N H_2SO_4, 90 °C temp. for 240 min	Total reducing sugar yield 26%	[54]
4.	Acid pretreatment	Cellulose and grass	1–10% H_3PO_4, 150–200 °C temp, 0–15 min	6.7% (w/w) xylose, 2.5% (w/w) arabinose and 6.1% (w/w) glucose of dry grass in 15 min at 170 °C and 2.5% H_3PO_4	[229]
5.	Acid pretreatment	Aspen, basam, fir, basswood, red maple and switchgrass	0.25–1% (w/v) H_2SO_4, 160–190 °C temp, 0–240 min	Maximum yield of xylose ranged from 70% (basam) to 94% (switch grass), glucose from 10.6% to 13.6%, and other minor sugars from 8.6% to 58.9%	[60]
6.	Acid pretreatment	Sugarcane, depithed bagasse and pith bagasse	1.2% (v/v) HCl, 121 °C temp for 4 h	Reducing sugar yield 37.21% for sugarcane depithed bagasse and 35.37% for sugarcane pith bagasse	[230]
7.	Acid pretreatment	Corn stover	0.25% (v/v) H_2SO_4, 121 °C temp. for 30–180 min	16.56% (w/w) xylose, 1.55% (w/w) arabinose and 3.36% (w/w) glucose dry raw material in 105 min at 121 °C and 2.13% (v/v) H_2SO_4	[231]
8.	Acid pretreatment	Olive tree	0–32% (w/w) H_2SO_4, 60–90 °C temp. for 0–240 min	30% (w/w) reducing sugars and 7% (w/w) glucose of dry raw material in 100 min at 90 °C and 31.8% (w/w) H_2SO_4	[66]
9.	Alkaline pretreatment	Wheat straw	2.15% H_2O_2 (v/v), pH 11.5, 35 °C temp. for 24 h	8.6% (w/v) monomeric sugars	[232]
10.	Alkaline pretreatment	Sorghum bicolor straw	2% NaOH, 60 °C temp. for 60–90 min	4.3-fold increase in total sugar with 2% NaOH at 60 °C for 90 min	[83]
11.	Alkaline pretreatment	Corn stover	0.5 g Ca $(OH)_2$, 55 °C temp. for 4 weeks, enzyme 15 FPU/g cellulose	Yield of glucose 93.2% and xylose 79.5%	[233]
12.	Alkaline pretreatment	Corn stover	Aquous ammonia, ammonia recycled percolation method	Reduced lignin content by 70–80%	[234]
13.	Steam explosion	Aspen chips	205 °C temp. for 3–10 min	Yield of xylose 10.3 g/100 dry chips with 3 minute	[235]
14.	Steam explosion	Lodgepole pine	SO_2-catalyzed steam explosion, 200 °C temp. for 5 min, 4% SO_2 (w/w)	Over all 77% ethanol yield	[236]
15.	Steam explosion	Salix	180–210 °C temp. for residence time (4,8 or 12 min), 0.25% or 0.5 % (w/w) H_2SO_4	55.6 g glucose and xylose per 100 g of raw material at 200 °C for 4 or 8 min using 0.5% H_2SO_4	[84]
16.	Steam explosion	Olive-tree pruning	190–240 °C temp. with impregnation by water or H_2SO_4 solution	Ethanol yield (7.2 g of ethanol/100 g of raw material) is obtained with water impregnated at 240 °C	[87]
17.	Steam explosion	Bamboo	3.53 MPa steam pressure for 5 min	215 ml of methane/g of exploded bamboo	[93]
18.	Steam explosion	Wheat straw	190 °C temp. for 10 min, 0.2% H_2SO_4	Recovery of glucose 102% and xylose 96%	[94]
19.	Steam explosion	Eucalyptus chips, wheat straw, *B. carinata* residue, sweet sorghum bagasse	190–210 °C temp. for 2–8 min	75–90% of xylose content	[95]
20.	LHW	Corn fiber	Temperature 160 °C for 20 min	Yield of 74% arabinose and 54% xylose	[108]
21.	LHW	Tifton 85 bermuda grass	Temperature (200–230 °C) with different pressure and time	Yield of 11.0 and 14.7 g/L ethanol with 200 and 230 °C treatment	[98]
22.	LHW	Wheat straw	Temperature (170 and 200 °C), residence time (0 and 40 min), solid concentration (5 and 10% (w/v)), pressure in reactor (30 bar), enzymatic hydrolysis using commercial cellulases	Sugar recovery (53% of content in raw material) and enzymatic hydrolysis (EH) yield (96% of theoretical)	[110]
23.	LHW	Wheat straw	Different process conditions	Recovery of 71.2% hemicelluloses-derived sugars (HDS) at 184 °C for 24 min, where as 214 °C for 2.7 min led to a maximum enzymatic hydrolysis (EH) yield of 90.6% of theoretical	[111]
24.	AFEX	Corn stover	Temperature of 90 °C, ammonia:dry corn stover mass ratio of 1:1, moisture content of 60% (dry weight basis), residence time of 5 min	Yield of 98% theoretical glucose, ethanol yield was increased up to 2.2 times over untreated samples	[114]
25.	AFEX	*Miscanthus giganteus*	Temperature 160 °C, 2:1 (w/w) ammonia to biomass loading, 233% moisture (dry weight basis) and 5 min reaction time, 15 FPU/(g of glucan) of cellulose and 64 p-NPGU/(g of glucan) of beta-glucosidase, xylanase and tween-80 as supplementation	95% glucan and 81% xylan conversions were achieved after 168 h enzymatic hydrolysis	[112]
26.	AFEX	Corn stover	Aqueous ammonia for soaking, period of 10–60 days at room temperature and atmospheric pressure, spezyme CP enzyme, simultaneous saccharification and fermentation with *S. cerevisiae* (D5A)	About 55–74% lignin removed, but retained nearly 100% of the glucan and 85% of xylan. 77% of ethanol yield based on glucan and xylan content	[115]
27.	AFEX	Switchgrass	Aqueous ammonia hydroxide (30%) with different liquid-solid ratios (5 and 10 ml/g) for either 5 or 10 days	40–50% delignification, cellulose content remain unchanged and hemicelluloses content decreased by approximately 50%	[113]
28.	CO_2 explosion	Aspen (hardwood) southern yellow pine (softwood)	Pretreatment with supercritical CO_2 (SC-CO_2) at 3100 and 4000 psi, temperature 112–165 °C for 10–60 min, moisture content 0–73% (w/w), enzymatic digestibility with commercial cellulase	Yield of 84.7 ± 2.6 and 27.3 ± 3.8% sugar at 3100 psi and 165 °C for 30 min. SC-CO_2 pretreatment with moisture content of 40,57, and 73% showed higher final sugar yields compared to without SC-CO_2	[237]

Table 1 (*continued*)

S. no.	Pretreatment method	Feed-stock	Pretreatment conditions	Yield	Refs.
29.	CO_2 explosion	Cellulose	Application of supercritical fluid to the hydrolysis of cellulose by the enzyme cellulose at pressure of 160 atm for 90 min at 50 °C temperature.	Glucose yield was 100% at supercritical conditions	[125]
30.	CO_2 explosion	Avicel	Treatment with supercritical CO_2 pressure with enzymatic hydrolysis	Accessible surface area increases, glucose yield by as much as 50%.	[124]
31.	CO_2 explosion	Avicel recycled paper mix, sugarcane bagasse, repulping waste of recycled paper	Under pressurized C0$_2$ at 35 °C for a controlled time period	More glucose (50%) is produced with increase of pressure compared to without the pretreatment	[238]
32.	Ionic liquids	Cellulose	Using ionic liquid (IL), 1-n-butyl-3-methylimidazolium chloride	The enzymatic hydrolysis rates were 50-fold higher for regenerated cellulose as compared to untreated cellulose	[136]
33.	Ionic liquids	Wheat straw and steam-exploded wheat straw (SEWS)	Using ionic liquid 1-butyl-3-methylimidazolium chloride, water used as control	Hydrolysis rate of wheat straw and SEWS reached at 70.37 and 100% with ionic liquids, while with water rate was 42.78 and 68.78%.	[239]
34.	Ionic liquids	Wheat straw	Using ionic liquid 1-ethyl-3-methyl-imidazolium diethyl phosphate, temperature 30 °C for 30 min fermentation with *S. cerevisiae*	Yield of reducing sugar reached at 54.8% after being enzymatically hydrolyzed for 12 h, ethanol production was 0.43 g/g glucose within 26 h	[142]
35.	Ionic liquids	Wood flour	Using ionic liquid 1-ethyl-3-methylimidazolium acetate, *Trichoderma viridae* cellulase	About 40% of lignin removed, cellulose crystallinity index dropped below 45, resulting in $>$90% of the cellulose in wood flour to be hydrolyzed by cellulase	[143]
36.	Organosolv process	Hybrid poplar chips	Temperature, time, catalyst dose and ethanol concentration using a composite (180 °C, 60 min, 1.25% H_2SO_4 and 60% ethanol) enzyme loading (20 filter units of cellulose/g cellulose)	About 82% of cellulose was recovered as monomeric glucose for 24 h, ~85% was recovered after 48 h hydrolysis	[240]
37.	Organosolv process	Beech wood chips	Bioorganosolv pretreatment by ethanolysis and white rot fungi for 2–8 weeks	Ethanol yield 0.294 g/g of ethanolysis pulp (74% of theoretical) and 0.176 g/g of beech wood chips (62% of theoretical), yield was 1.6 time higher than fungal pretreatment	[241]
38.	Organosolv process	*Pinus radiate* D. Don	Temperature 195 °C, 5 min, pH 2.0 and acetone:water 1:1 of ratio	Yield of 99.5% ethanol	[57]
39.	Organosolv process	Softwood pulp	Pulp with lignin 6.4–27.4% (w/w), temperature of 48 h, enzyme loading of 40 filter paper units/g cellulose	About $>$90% conversion with 48 h	[242]
40.	Ozonolysis	Wheat and rye straw	Ozonated wheat and rye straw under room condition	Yields of up to 88.6 and 57% compared to 29 and 16% in non-ionated wheat and rye straw	[152]
41.	Ozonolysis	Activated sludge	Oxidative ozone pretreatment with anaerobic sludge digestion	Solubilization of 19 and 37% of the solids lead to high methane recovery	[243]
42.	Wet oxidation	Softwood (*Picea abies*)	Temperature 200 °C for 10 min at neutral pH	Highest yield of about 79% of theoretical in 72 h	[157]
43.	Wet oxidation	Corn stover	Alkaline and acidic wet oxidation (WO) (195 °C, 15 min and 12 bar oxygen) enzyme cellulases added at 50 °C.	About 22, 29 and 83% of the theoretical ethanol yield with enzyme loading of 73, 76 and 43.5% FPU/g cellulose.	[158]

interest has been directed towards a biological method, and recent studies show the increasing interest in this direction [46–48].

The microorganisms, mainly brown-, white- and soft-rot fungi, actinomycetes and bacteria, which degrade lignin, hemicelluloses and very little of cellulose have been reported by various researchers [9,43,49,50]. Several white-rot fungi such as *Phanerochaete chrysosporium*, *Ceriporia lacerate*, *Cyathus stercolerus*, *Ceriporiopsis subvermispora*, *Pycnoporus cinnarrbarinus* and *Pleurotus ostreaus* have showed high delignification efficiency on different lignocellulosic biomass [51–53]. Lignin delignification by these fungi takes weeks to achieve significant results but have been found to be very selective and efficient.

4. Exploration of chemical pretreatment

Lignin forms a protective shield around the cellulose and hemicelluloses, and protects these polysaccharides from enzymatic degradation, though the cellulose and hemicelluloses must be readily available to lignocellulosic enzymes for its degradation to monomers [54,55]. Thus, the cellulose becomes vulnerable to enzymes after removal of lignin and thereafter the fermentable sugars i.e. glucose can then be fermented into derived products [56]. Therefore, a pretreatment must be applied to remove lignin, decrease cellulose crystallinity, and increase the surface area for enzymatic activity. Chemical, physical and physico-chemical pretreatments are the most studied pretreatment techniques among all reported pretreatment methods. Some common chemical or physico-chemical pretreatment techniques including acid, alkaline, steam explosion, liquid hot water, ammonia fiber, carbon dioxide explosion, ionic liquids, organosolv, ozonolysis and wet oxidation pretreatments are explored in this section. The different types of chemical and physico-chemical pretreatment processes are summarized in Table 1.

4.1. Acid pretreatment

Acid pretreatment of lignocelluloses is a very effective and well-known process to obtain a structure suitable for enzymatic hydrolysis. Lignocellulosic ethanol production involving acid hydrolysis followed by enzymatic saccharification using cellulase enzyme has been reported by most of the researchers [57–59]. Acid pretreatment depends on parameters such as type of acid, acid concentration, solid to liquid ratio and temperature. Inorganic acids such as sulfuric acid, nitric acid, hydrochloric acid and phosphoric acid have been elaborated for lignocellulosic pretreatment. Pretreatment using sulfuric acid has been extensively studied because of its high catabolic activity. Some organic acids such as paraacetic acid, maleic acid, etc. have also been studied for

pretreatment [27,60,61]. The different acid pretreatment processes for various feedstocks have been summarized in Table 1.

Acid pretreatment requires high temperature and pressure for effective pretreatment. Also dilute acid pretreatment is the most effective process for lignocelluloses, which generates lower degradation products than concentrated acid pretreatments [34,62]. It can be used either as a pretreatment of lignocelluloses for enzymatic hydrolysis, or as the method for hydrolyzing the lignocelluloses to fermentable sugars in two-stage acid hydrolysis. Dilute acids ranging from 0.1% to 2% (w/v) are generally used in the acid pretreatment methods. Wang et al. [63] reported 80% conversion of cellulose present in eucalyptus wood chips. Zhu et al. [64] obtained about 40% of cellulose conversion, when spruce wood chips were pretreated at 180 °C with an acid concentration of 1.84% followed by disk milling. However, acid pretreatment is less attractive due to the formation of inhibitory compounds, equipment corrosion, toxic nature, and high operational and maintenance costs [65,66].

Acid pretreatment allows to hydrolyze the hemicelluloses, especially xylan present in the lignocelluloses. Hemicelluloses can be degraded into xylose, mannose, acetic acid, galactose, glucose, etc. At the high temperatures and pressures often used in the industrial processes, glucose and xylose degrade into degradation products such as furfural and hydroxymethyl furfural, respectively and further degradation forms formic acid and levulinic acid. Phenolic compounds are also formed during pretreatment from the partial breakdown of lignin [27,67,68]. All these compounds have negative effects on the downstream processes. Therefore, removal of these compounds is essential, which also increases the process cost.

4.2. Alkaline pretreatment

Alkaline pretreatment is one of the extensively studied chemical pretreatment methods, which employs various alkali compounds such as sodium hydroxide [69,70], calcium hydroxide (lime) [71], potassium hydroxide [72,73], aqueous ammonia [74,75], ammonium hydroxide [76,77] and hydrogen peroxide or combination of these [78]. The alkaline pretreatment process has been summarized in Table 1.

Alkaline pretreatment removes acetyl group and various uronic acid substitutions in hemicelluloses that increase the accessibility of hemicelluloses and cellulose to hydrolytic enzymes [33]. During alkaline pretreatment, the reactions salvation and saphonication take place, which cause swelling, leading to decrease in the degree of polymerization and crystallinity, increase in internal surface area, disruption of the lignin structure and breaking of the structural linkages between lignin and carbohydrates [20,79]. Among the chemical pretreatments, alkali pretreatment provides the most effective method for breaking the ester bonds between lignin, hemicellulose and cellulose, and avoids fragmentation of the hemicellulose polymers [80].

The alkaline pretreatment reflects many advantages from numerous studies. Sodium hydroxide has been reported to increase the hardwood digestibility from 14% to 55% by reducing lignin content from 24–55% to 20% [13]. Calcium hydroxide (also known as lime) was found to be effective to remove acetyl groups from hemicelluloses, reduce steric hindrance of enzymes and enhance the cellulose digestibility [33]. This effect was observed for enzymatic hydrolysis of corn stover [81] and poplar wood [82], when the biomass was pretreated using lime and the temperature was varied from 85 to 150 °C for 3–13 h. High rate of enzymatic saccharification and further ethanol production were observed, when wheat and sorghum straws were pretreated using dilute alkaline [83]. However, a significant disadvantage of alkaline pretreatment was found to be converted into irrecoverable salts, and/or the incorporation of salts into the biomass during the pretreatment process. The treatment of large amount of salts has become a challenging issue for alkaline pretreatment [33].

4.3. Steam explosion

Steam explosion is a physico-chemical pretreatment, which is nowadays a most widely employed method for treating the lignocellulosic biomass [84,85]. During the treatment, the material is treated with steam at a high temperature for few minutes to facilitate subsequent enzymatic hydrolysis of cellulose and hemicellulose to monomeric hexose and pentose sugars. The material is also impregnated with an acid prior to steam explosion to increase the overall sugar yield. Steam explosion is typically performed at a temperature range of 160–260 °C (corresponding pressure, 0.69–4.83 MPa) for few seconds to few minutes and further the material is exposed to the atmospheric pressure [86]. Cara et al. [87] studied the production of ethanol by simultaneous saccharification and fermentation from olive-tree pruning through steam-explosion pretreatment at different temperatures (190–240 °C) after impregnation of pruning by water or sulfuric acid solution. They obtained maximum ethanol yield of 72 g of ethanol/kg of raw material from water-impregnated residue, which was steam exploded at a temperature of 240 °C.

The factors that affect steam explosion pretreatment are residence time, temperature, biomass size, and moisture content [88]. Addition of H_2SO_4 (or SO_2) or CO_2 [typically 0.3–3% (w/w)] in steam explosion decreases time and temperature of reaction, improves hydrolysis rate, decreases the production of inhibitory compounds, and leads to complete removal of hemicelluloses [89]. It is revealed by varying wood chip size from 2 to 12 mm that the biomass size also affects the performance of steam explosion [85]. Significant effect of biomass size on hemicellulosic sugar recovery and enzymatic saccharification was also observed by Zhu et al. [30], when wood chips size was varied from 0.6 to 50 mm.

Steam explosion has been explained extensively for a large number of different lignocellulosic feedstocks (Table 1). Grous et al. [90] reported an efficiency of 90% in enzymatic hydrolysis of poplar chips pretreated by steam explosion, compared to only 15% hydrolysis of untreated chips. Steam explosion allows removing the lignin to a limited extent and redistributes the lignin on the fiber surfaces as a result of melting and depolymerization/repolymerization reactions [91]. Viola et al. [92] reported the steam-explosion treatment of wheat, barley and oat straws on the basis of carbohydrate recovery. The yield of fodder, lignin and hemicelluloses was found to be dependent on the nature of the raw straw. Kobayashi et al. [93] extended the use of steam-explosion technique, primarily to improve the anaerobic digestion of bamboo into biogas and reported the maximum 215 ml of methane/g of steam exploded bamboo at a steam pressure of 3.53 MPa for 5 min. However, Linde et al. [94] investigated ethanol production by exploding wheat straw with steam at 190 °C for 10 min using low concentration of sulfuric acid (0.2%) prior to pretreatment. Further, simultaneous saccharification and fermentation (SSF) was performed at a low enzyme loading, 3–14 FPU g^{-1} water-insoluble solids (WIS) and low yeast concentration of 2 g/L, and resulted in the highest recovery of glucose (102%), xylose (96%) and ethanol yield (189 g/kg dry straw). Ballesteros et al. [95] also applied steam explosion to poplar and eucalyptus chips at 210 °C for 4 min; wheat straw at 190 °C for 8 min; *Brassica carinata* residue at 210 °C for 8 min; and sweet sorghum bagasse at 210 °C for 2 min, which resulted in the solubilization of the hemicelluloses by 75–90%, depending on the nature of the substrate.

Steam explosion pretreatment is found to be advantageous due to low energy requirement and no recycling or environmental costs. The conventional mechanical methods require 70% more

energy than steam explosion to achieve the same particle size reduction. Further, steam explosion is recognized as one of the most cost-effective pretreatment processes for hardwoods and agricultural residues, but it is less effective for softwoods [96,24]. Steam pretreatment using a catalyst has been claimed to be the closest to the commercialization [89]. Steam explosion also has some limitations including destruction of a portion of the xylan fraction, incomplete disruption of the lignin–carbohydrate matrix, and generation of compounds that might be inhibitory to microorganisms used in fermentation processes [97].

4.4. Liquid hot water (LHW)

LHW pretreatment is similar to steam explosion except for the use of water in the liquid state at elevated temperatures (160–240 °C) instead of steam. LHW results in hydrolysis of lignocelluloses, removal of lignin, rendering cellulose in the biomass more accessible while avoiding the formation of inhibitory compounds that occur at higher temperatures [98]. However, complete delignification is not possible by hot water alone due to the recondensation of soluble components originated from lignin. This pretreatment offers several advantages, i.e. (i) it does not include any catalyst or chemical, (ii) it requires low temperature, (iii) it minimizes degradation products, (iv) it eliminates the requirement of washing step or neutralization, (v) it has low cost of the solvent for large scale applications [99–101]. Additionally, biomass size reduction is not required because the particles are broken down during pretreatment, which makes the process more attractive for large scale [102,103]. The LHW pretreatment process for various feedstocks has been summarized in Table 1.

The hot water cleaves hemiacetal linkages, thus, liberating acids during biomass treatment, which facilitates the breakage of ether linkages in biomass. It is stated that the cleavage of O-acetyl groups and uronic acid substitutions on the hemicellulose could help or hinder LHW pretreatment because of the release of these acids. These acids act as a catalyst, and catalyze the formation and removal of oligosaccharides, and further hydrolyze hemicellulose to monomeric sugars, which can be subsequently degraded to aldehydes (i.e. furfural from pentoses and HMF from hexoses) [104,105]. The formation of monosaccharides and subsequent degradation catalyze the hydrolysis of cellulosic material. Autocatalytic formation of inhibitory compounds can be minimized by maintaining the pH between 4 and 7 [106]. Mosier et al. [107] reported the pretreatment of corn stover with LHW at 190 °C for 15 min under controlled pH and obtained 90% conversion of cellulose by subsequent enzymatic hydrolysis. LHW pretreatment at 160 °C and pH above 4.0 can dissolve 50% of the fibers from corn fibers in 20 min [106]. It has been found to remove up to 80% of the hemicellulose and to enhance the enzymatic digestibility of pretreated corn fiber [108] and sugarcane bagasse [109]. Further, Perez et al. [110] used LHW to pretreat wheat straw and obtained maximum hemicellulose-derived sugar recovery of 53% and enzymatic hydrolysis yield of 96%. Perez et al. [111] continued to optimize process variables (temperature and residence time) in LHW pretreatment of wheat straw and achieved 80% xylose recovery and 91% enzymatic hydrolysis.

4.5. Ammonia fiber explosion (AFEX)

Ammonia fiber explosion is a physico-chemical pretreatment process in which lignocellulosic biomass is exposed to liquid ammonia at high temperature and pressure for a period of time, and then the pressure is suddenly reduced [112,113]. The parameters that affect AFEX process are ammonia loading, temperature, water loading, blowdown pressure, time and number of treatments [114]. Ammonia has a remarkable effect on lignocelluloses causing swelling and physical disruption of biomass fibers, partial decrystallization of cellulose, and breakdown of lignin–carbohydrate linkages [115,116]. During the pretreatment, only a small amount of solid material solubilizes that ensures loss of almost no hemicelluloses or lignin. AFEX pretreatment changes the structure of biomass, which increases water holding capacity and digestibility of biomass [117]. AFEX pretreatment process for various feedstocks has been summarized in Table 1.

AFEX pretreatment possesses numerous advantageous as it does not form any toxic materials [116], does not require reduction of particle size [33], does not require conditioning for fermenting microbes [118], gives about 99% recovery of sugars, and does not require addition of nitrogen source for fermentation as residual ammonia serves as a nitrogen source. The process could be significantly demonstrated for the saccharification and fermentation rate of various herbaceous crops and grasses as compared to woody biomass [34]. Recently, AFEX pretreatment has been successfully used in simultaneous saccharification and co-fermentation (SSCF) processes using recombinant *Saccharomyces cerevisiae* and *Escherichia coli* strains obtaining high ethanol yields from switchgrass and corn stover, respectively [119,120]. However, the recent studies showed that the part of phenolic fragments of lignin and other cell wall extractives may remain on the cellulosic surface, which can further be washed with water [116]. Furthermore, ammonia can be recycled after the AFEX pretreatment, which enhances the process viability through cost reduction and environmental protection [121]. However, it is not a very effective for lignocellulosic biomass with relatively high lignin content such as woody biomass, nut-shells and other high-lignin feedstocks [34].

4.6. Carbon dioxide explosion

Carbon dioxide can also be used for the pretreatment of lignocelluloses. CO_2 is used as a supercritical fluid under high pressure, where lignin gets solubilized effectively [122]. Under the high pressure, CO_2 penetrates the biomass and results in the increased digestibility of biomass. It is believed that once CO_2 dissolves in water, it will form carbonic acid, which catalyzes the hydrolysis of hemicellulose. Release of the pressurized gas in the digester results in the disruption of the structural biomass and increases the accessible surface area to enzymes [123]. The low cost of carbon dioxide as a pretreatment solvent, no generation of toxins, use of low temperatures and high solids capacity are attractive features of this pretreatment. However, the high cost of equipment that can withstand high-pressure conditions of CO_2 pretreatment is a great limitation to the application of this process in large scale.

Explosion pretreatment of the cellulosic materials by supercritical carbon dioxide has been studied by several researchers (Table 1). According to Zheng et al. [124], high pressure is desirable for fast penetration of the CO_2 molecules into the cellulosic pores, which leads to high glucose yield. Park et al. [125] studied simultaneous pretreatment by CO_2 explosion and enzymatic hydrolysis and obtained 100% glucose yield. Zheng and Tsao [126] showed the stability of cellulosic enzymes under supercritical CO_2 at a temperature of 35 °C. It was shown that supercritical CO_2 in the presence of water could efficiently improve the enzymatic digestibility of aspen (hardwood) and southern yellow pine (softwood) [127].

4.7. Ionic liquids (ILs)

The use of ILs as solvent for pretreatment of lignocellulosic biomass has received great attention during the last decade [128–130]. ILs are new class of solvents with low melting points (< 100 °C), wide liquid temperature range, high

thermal and chemical stability, non-flammability, negligible vapor pressure, consisting of ions (cations and anions) and good solvating properties [131,132]. The dissolution mechanism of cellulose in ILs involves the oxygen and hydrogen atoms of cellulose hydroxyl groups and forms electron donor–electron acceptor (EDA) complexes, which interact with ILs. The hydrogen bonds between molecular chains of the cellulose are broken down on interaction of cellulose-OH and ILs, and result in the dissolution of cellulose [133,134].

Imidazonium salts such as N-methylmorpholine-N-oxide monohydrate (NMMO) [135], 1-n-butyl-3- methylimidazolium chloride (BMIMCl) [136,137], 1-allyl-3- methylimidazolium chloride (AMIMCl) [138], 3-methyl-N-bytylpyridinium chloride (MBPCl) and benzyldimethyl (tetradecyl) ammonium chloride (BDTACl) [139] have been widely studied in the fractionation of biomass. ILs 1-allyl-3-methylimidazonium chloride (AMIMCl) and 1-butyl-3-methylimidazonium chloride (BMIMCl) are found to be very effective as non-derivatizing solvents for the dissolution of cellulose at temperatures below 100 °C [140]. The ionic liquid pretreatment processes for various feedstocks has been summarized in Table 1. Using 1-butyl-3-methylimidazolium chloride (BMIMCl) for pretreatment, Dadi et al. [136] found that the initial enzymatic hydrolysis rate and yield of pretreated Avicel-PH-101 could be increased by 50- and 2-fold, respectively, in comparison with untreated Avicel. Kuo and Lee [135] also obtained 2-fold higher enzymatic hydrolysis yield as compared to untreated bagasse, when the sugarcane bagasse was treated with 1,3-N-methylmorpholine- N-oxide (NMMO).

A variety of ILs has been identified for their potential to enhance the digestibility of lignocellulosic biomass [132,141]. Most available data have showed the effectiveness of ILs, which can be used to pretreat lignocellulosic biomass such as bagasse [136], wheat straw [142], wood [143], etc. In general, these ILs have also been considered to be environment friendly [144]. However, details of processing of lignocellulosic biomass with ionic liquids are still under investigation.

4.8. Organosolv process

The organosolvation method has attracted attention and has demonstrated potential for utilization in lignocellulosic pretreatment. In this process, a mixture of organic solvents with inorganic acid catalysts (HCl or H_2SO_4) in aqueous form is used to break down the internal lignin and hemicellulose bonds [145]. Organic acids such as oxalic, salicylic and acetylsalicylic acids can also be used as a catalyst in the organosolvation process [146]. The solvents commonly used in the process are methanol, ethanol, acetone, ethylene glycol, triethylene glycol, glycerol, aqueous phenol, aqueous n-butanol, tetrahydrofurfuryl alcohol, etc. [20]. Due to the high cost of the solvents, ethanol and methanol are preferred over alcohols of higher boiling points such as ethylene glycol, tetrahydrofurfuryl alcohol, etc. [147]. The usual operation temperature of organosolv falls in the range of 150–200 °C. The organosolv pretreatment process for various feedstocks has been summarized in Table 1. However, Araque et al. [57] found higher ethanol yield, about 99.5%, after organosolv pretreatment at a temperature of 195 °C and pH 2.0 in 5 min. Arato et al. [147] used lignol process to treat woody biomass using water and ethanol under selected conditions and observed numerous chemical reactions during the process, which resulted in splitting of biomass into various compounds.

This process removes lignin extensively and results in almost complete hemicellulose solubilization by hydrolyzing the internal lignin bonds as well as ether and 4-O-methylglucuronic acid ester bonds between lignin and hemicellulose and hydrolyzes glycosidic bonds present in hemicellulose and partially in cellulose depending on process parameters [145]. In general, complete solvent (ethanol) recovery is a critical issue to the process economy, because it may be inhibitory to the enzymatic hydrolysis, and fermentation or anaerobic digestion [96,148]. Solvents used in the process need to be drained from the reactor, evaporated, condensed and/or recycled to reduce the operational costs. The simultaneous optimization of all unit operations is a fundamental task to make a cost-effective organosolv process [149].

4.9. Ozonolysis

Ozone treatment is a way of reducing the lignin content in lignocellulosic wastes [150]. The main parameters in ozonolysis are moisture content of the sample, particle size and ozone concentration in the gas flow. It has an advantage that the process is carried out at room temperature and normal pressure, and does not lead to the formation of any inhibitory compound [151,152]. However, ozonolysis requires a large amount of ozone, which makes the process expensive [96].

Ozonolysis has been studied to degrade lignin and hemicellulose in many lignocellulosic materials such as wheat straw [153], rye straw [152], bagasse, green hay, peanut, pine [151], cotton straw [69] and poplar sawdust [154]. The ozonolysis pretreatment process for various feedstocks has been summarized in Table 1. In a study, the rate of enzymatic hydrolysis could be increased by a factor of 5 followed by 60% removal of the lignin from wheat straw using ozone pretreatment. Enzymatic hydrolysis yield could be increased up to 57% and lignin could be decreased from 29% to 8% after ozonolysis pretreatment of poplar sawdust [155]. Ozonolysis pretreatment for biogas production was investigated to improve the digestion of sewage-activated sludge [20] and olive mill waste [156].

4.10. Wet oxidation

Wet oxidation is an oxidative pretreatment method in which oxygen or air is employed as a catalyst at temperature above 120 °C [157,158]. Reaction temperature, time and oxygen pressure are the most important parameters in wet oxidation [159]. The main reactions that occur in wet oxidative pretreatment are oxidative reactions as well as the formation of acids. This process is effective in separation of the cellulosic fractions from lignin and hemicelluloses [160].

Several studies have been carried out on wet oxidation as a pretreatment strategy on different substrates [161]. The wet oxidation pretreatment process for various feedstocks has been summarized in Table 1. Lissens et al. [162] used wet oxidation process at 185–220 °C and 0–12 bar oxygen pressure for 15 min and obtained increased yields of methane by approximately 35–70% from raw and digested lignocellulosic biowastes. Martin et al. [163] studied wet oxidation as a pretreatment method for enhancing the enzymatic digestibility of sugarcane bagasse and found highest sugar yield at 185 °C in 5 min. Pedarson et al. [164] obtained glucose and xylose yields of 400 and 200 g/kg, respectively, from wet oxidation treated wheat straw in 24 h at 50 °C using an enzyme mixture of 36 FPU/g celluclast 1.5 L and 37 CBU/g of Novozyme-188. Further, this technology would widely be used for ethanol production through simultaneous saccharification and fermentation (SSF) from corn stover [165], clover-ryegrass [166] and olive pulp [167].

5. Parameters for pretreatment

The complexity of any biomass reflects in the relationship between its structural and carbohydrate components. The researchers

have concluded that crystallinity of biomass is just a factor, which influences the breakdown of biomass. Other factors that influence the biomass hydrolysis are degree of polymerization (DP), accessible surface area, environmental impact, economic assessment and protection by lignin and hemicelluloses content [15,32]. These factors are summarized briefly in this section.

5.1. Biomass crystalinity

Different types of biomass from woody plants, herbaceous plants, grasses, aquatic plants, agricultural crops and residues, municipal solid waste and manures contains different compositions of cellulose, hemicellulose, lignin and other extractives [39]. However, the main components are three the polymers namely cellulose, hemicelluloses and lignin. These polymers are associated with each other in a hetero-matrix to different degrees and varying relative composition depending on the type, species and even source of the biomass [168]. The cellulose in any biomass is found to be present in two forms namely amophorous and crystalline.

The crystalline cellulose core of cell-wall microfibrils is highly resistant to chemical and biological hydrolysis because of its structure, in which chains of cellodextrins are precisely arranged. It is widely studied that decrease in the crystallinity increases the digestibility of lignocelluloses. The hydrophobicity of crystalline cellulose makes it resistant to the acid hydrolysis because it forms a dense layer of water near the hydrated cellulose surface. The strong interchain hydrogen-bonding network also makes crystalline cellulose resistant to enzymatic hydrolysis, whereas hemicelluloses and amorphous cellulose are readily digestible [169]. On the contrary, some studies have showed more digestibilities of more crystalline lignocelluloses. Kim and Holtzapple [170] found that the degree of crystallinity of corn stover increased from 43% to 60% through delignification with calcium hydroxide due to removal of amorphous components (lignin and hemicellulose). Zhang and Lynd [171] also explained that a slower conversion of crystalline cellulose as compared to amorphous cellulose could increase the percentage crystallinity of the hydrolyzed biomass. However, an increase in crystallinity of pretreated material could not negatively affect the enzymatic hydrolysis.

5.2. Degree of polymerization

The degree of polymerization and cellulose crystallinity have been considered as important factors in determining the hydrolysis rates of relatively refined cellulosic substrate [172]. In the enzymatic hydrolysis, endoglucanases target at internal sites of the cellulose chains, which is primarily responsible for decreasing the degree of polymerization of cellulosic substrates [43]. The effect of different pretreatments on cellulose chain length has been studied in the reduction of the degree of polymerization in solids prepared after different pretreatments. It is suggested that hemicelluloses removal had a more severe impact on cellulose chain length than lignin removal [154].

5.3. Accessible surface area

The improvement in enzymatic hydrolysis by removing lignin and hemicelluloses is related to the cellulose accessible surface area. The enzymatic hydrolysis involves a heterogeneous catalytic reaction with a direct physical interaction between the enzyme molecules and cellulose. Therefore, the accessible surface area in lignocellulosic material plays an important role in enzymatic hydrolysis [173].

Surface area in lignocellulosic materials can be categorized into external and internal surface area. The external surface area is related to the size and shape of the particles, while, the internal surface area depends on the capillary structure of cellulosic fibers. The accessible surface area changes during enzymatic hydrolysis and correlates with crystallinity or lignin protection or hemicellulose presentation or all of them [20]. Some studies have described a good correlation between the pore volume or population (accessible surface area for cellulases) and the enzymatic digestibility of lignocellulosic materials. Maclellan [174] and Yang et al. [175] concluded that the pore size of the substrate plays a limiting factor in the enzymatic hydrolysis of biomass. Removal of hemicellulose increases the mean pore size of the substrate, and therefore, increases the probability of the cellulose to get hydrolyzed [22]. Drying of pretreated lignocellulose can cause a collapse in pore structure, resulting in a decreased enzymatic hydrolysis rate [175]. Further, cellulases can also be trapped in the pores of substrate, if the internal area is much larger than the external area, which is the case for many lignocellulosic biomass [39]. However, it is shown that the cellulose surface area is not a major limiting factor for hydrolysis of pure cellulose [176].

5.4. Lignin and hemicellulose contents

The relationship among structural and compositional factors reflects the complexity of the lignocellulosic biomass matrix. The variability of these characteristics can be explained perfectly by enzymatic digestibility of different types of biomass. Generally, plant biomass contains 40–50% cellulose (with exception to a few plants, such as cotton and hemp bast-fiber that are made up of $\approx$80% cellulose), 20–40% hemicellulose, and 20–30% lignin by weight [39]. The presence of lignin and hemicelluloses makes the access of cellulose to cellulolytic enzymes difficult, thus, reducing the efficiency of enzymatic hydrolysis [22]. Lignin restricts the rate and extent of enzymatic hydrolysis by acting as a shield, and prevents the digestible parts of the biomass from being hydrolyzed [177]. Thus, lignin content and its distribution constitute the most recognized factors which are responsible for recalcitrance of lignocellulosic materials to enzymatic degradation by limiting the substrate accessibility. Therefore, the delignification processes can improve the rate and extent of enzymatic hydrolysis [178]. However, the solubility of the lignin in acid, neutral or alkaline environments depends on the precursors of the lignin namely *p*-coumaryl, coniferyl, sinapyl alcohol or combinations of them [179].

Among the key components of lignocelluloses, hemicelluloses are the most thermo-chemically sensitive [22]. It is a complex carbohydrate structure, which serves as a bridge between lignin and cellulose fibers, and gives the whole cellulose–hemicellulose–lignin network more rigidity [180]. The dominant component of hemicelluloses is xylan in hardwoods and agricultural plants and grasses, while glucomannan in softwoods. The hemicelluloses reduce the mean pore size of the biomass, and therefore reduce the accessibility of cellulose to hydrolytic enzymes. The xylan in hemicelluloses can be extracted quite well in an acid or alkaline environment, while glucomannan can hardly be extracted in an acid environment and needs a stronger alkaline environment than xylan [181]. Further, severity parameters must be carefully optimized to avoid the formation of hemicellulose degradation products such as furfurals and hydroxymethyl furfurals, which have been reported to inhibit the fermentation process [182].

6. Formation of inhibitors

The chemical pretreatment of biomass involves several harsh and severe thermo-chemical treatments, which resulted in the conversion of phenolic compounds (lignin) and sugars present in the plant materials to degradation compounds. Presence of these

degradation compounds inhibits the fermentation process [11]. The nature and concentration of the degradation compounds depend on the raw material (agricultural and forestry residues), the pretreatment method and conditions employed such as temperature, residence time, pressure, pH, etc. [183,184]. These compounds have been grouped into four categories: (i) furan derivatives (furfural and HMF), (ii) carboxylic acids, (iii) phenol derivatives, and (iv) heavy metal ions released by corrosion of the digester.

6.1. Furan derivatives

Furfural and 5-hydroxymethyl furfural (HMF) are the only furans, which are usually found in the hydrolyzates in significant amounts. These compounds are formed by decomposition of pentoses and hexoses [185,186]. Among the others, sulfuric acid pretreatment of lignocellulosic biomass produces sugar degradation byproducts [187].

Furfural formed easily during high temperature process as compared to HMF. Hence, furfural is found in large quantity in the hydrolysates. Furfural also has stronger toxicity on ethanol fermentation than other inhibitors [188]. *In-vitro* activity of several important enzymes in the primary carbon catabolism, such as hexokinase, aldolase, phosphofructokinase, triosephosphate dehydrogenase, and alcohol dehydrogenase, furfural was found to be more inhibitory. Among these enzymes, triosephosphate and alcohol dehydrogenases have been found to be the most sensitive. However, the inhibition of certain non-glycolytic enzymes, such as pyruvate and aldehyde dehydrogenases is even more severe [189]. Consequently, cell growth is more sensitive in the presence of furfural than the ethanol formation. In some cases, it is also found that furfural is converted to less inhibitory compounds, furfuryl alcohol and furoic acid by some yeast species [190].

HMF is not severely toxic in nature as compared to furfural. This is in line with the observation that the *in-vitro* inhibition of the enzymes such as pyruvate and aldehyde dehydrogenases, HMF had the lower inhibitory effect than furfural. However, it was also reported that HMF increases the lag phase and decreases the cell growth [191]. On the other hand, the conversion rate of furfural was found to be about 4 times faster than that HMF. Hence, HMF remains much longer than furfural in the medium, and consequently, HMF makes the microbial process last longer than that of furfural [192].

Mussatto and Roberto [193] reported that a synergistic effect occurs, when these compounds are combined with several other compounds formed during lignin degradation. However, Taherzadeh and Karimi [20] reported that no furfural or HMF (inhibitory sugar degradation products) was detected in hydrolysate obtained with alkaline peroxide pretreatment, which favors the ethanol fermentation. Further, severity parameters must be carefully optimized to avoid the formation of hemicellulose degradation products.

6.2. Carboxylic acids

Acetic, formic and levulinic acids are the most commonly used carboxylic acids, which are found in the hydrolyzates. These acids are released due to the hydrolysis of the acetyl groups linked to the sugar or other linkage present in hemicellulosic backbone [194]. Acetic acid is not only a by-product of hydrolysis [195], but also a well-known by-product of fermentation [196]. It generates from the hydrolysis of the acetyl groups in the hemicelluloses, and its generation mainly depends on the temperature and residence time of pretreatment until the acetyl groups are fully hydrolyzed. It is reported that the baker's yeasts can tolerate up to about 5 g/L concentration of acetic acid is undissociated form [197]. It is generally observed that undissociated form of the acetic acid largely affects microorganisms than dissociated form [198] because, undissociated carboxylic acids diffuse through the microbial cell membrane, dissociate and decrease the internal pH [7]. According to Van Niel et al. [199], an acetic acid concentration of 4.4 g/L in the culture medium can cause 15% inhibition of the growth of *Caldicellulosiruptor saccharolyticus*. This is in agreement with the findings of Panagiotopoulos et al. [200], who used biomass-derived sugars from wheat and barley straws, and observed better fermentability to hydrogen production with acetic acid concentrations up to 1.0 g/L, and inhibitory effect with acetic acid concentration more than 3 g/L. Moreover, the formic acid also formed due to the breakdown of furan derivatives, which is much more inhibitory than acetic acid [185]. According to Redding et al. [184], the formic and levulinic acids, generated during acid pretreatment of coastal Bermuda grass at temperatures lower than 180 °C, were found to be much lower than the reported inhibitory level (> 200 mM).

6.3. Phenol derivatives

Phenolic/aromatic compounds are produced by the degradation of lignin during pretreatment of biomass. However, the aromatic compounds may also form as a result of sugar degradation and are present in lignocelluloses as extractives. The inhibition mechanisms of these compounds in the fermentation process have not yet been completely elucidated [201]. Some researches indicated that these compounds promote a loss of integrity in biological membranes, and thus affect their ability as selective barriers, as enzyme matrices, decrease cell growth and further sugar assimilation [202]. It was established that low molecular weight phenolic compounds are more inhibitory than those with high molecular weight. Furthermore, the substituent position of functional group in phenolics also influences toxicity of these compounds [203]. Among the phenolic compounds, syringaldehyde and vanillic acid affect the cell growth [204] and the ethanolic fermentative metabolism of several microorganisms, such as *Pichia stipitis, Candida shehatae* and *S. cerevisiae* [4].

7. Inhibitory effect on microbial processes

The degradation products as mentioned earlier inhibit the fermentation by different mechanisms. However, a combination of the action of several compounds other than sugars present in the hydrolysate may be one of the reasons for the inhibition of the process [205,206].

The inhibitory effect of degradation compounds on alcohol dehydrogenase (ADH), pyruvate dehydrogenase (PDH) and aldehyde dehydrogenase (ALDH) obtained from *S. cerevisiae* was found. Furthermore, these compounds caused DNA breakdown, which resulted in the inhibition of RNA and protein synthesis [189]. In a study, Almaida et al. [185] found that furan derivatives damaged the cell walls and the cell membranes. However, the inhibition effect of these compounds depends on the concentration of inhibitors in the broth [207]. It was demonstrated that *S. cerevisiae* and *P. stipitis* strains were more sensitive to inhibition by furfural than HMF at the same concentration, while the presence of both furfural and HMF suppressed the cell growth [207]. Nigam [208] also found that a furfural concentration of 1.5 g/L interfered in respiration and growth of *P. stipitis*. Delgenes et al. [209] also showed that the growth of *P. stipitis* was reduced by 43%, 70% and 100% in presence of HMF concentration of 0.5, 0.75 and 1.5 g/L, respectively.

8. How to overcome these inhibitors?

To overcome the inhibitory effect on fermentation process, either the hydrolysate needs to be detoxified or microorganisms can be adapted to these inhibitory compounds. Detoxification of hydrolysate is very expensive; hence, adaptation of microorganisms to the inhibitory compounds seems to be very effective.

8.1. Adaptation of microorganisms

Adaptation of microorganisms to inhibitors present in the lignocellulosic hydrolysates has been proven to get the improved ethanol yields and to reduce the lignocellulosic ethanol production cost by removing detoxification step [205]. In a traditional chemostat process, the presence of inhibitors such as furfural can be tolerated only at low concentrations and low dilution rates [210]. However, if the cells remain in the bioreactor through immobilization [211] or encapsulation [212], it would be possible to achieve a higher dilution rate in a continuous cultivation. Talebnia and Taherzadeh [212] showed that the cells present in a capsule could protect itself against the inhibitors during cultivation in toxic hydrolyzate.

Cantarella et al. [213] reported the increase of ethanol production during the fermentation of poplar wood hydrolysate in the presence of acetic acid, vanillin and HMF. Recently, it was demonstrated that *P. stipitis* reduces the aldehyde group in the furan ring of HMF and furfural [207], and was able to consume acetic acid during fermentation [214]. However, some species of *S. cerevisiae* have the capacity to transform furfural and HMF into less toxic compounds of furfuryl alcohol and 2,5-bishydroxymethylfuran, respectively. This process is also known as “in-situ detoxification” [215]. Also it was noticed that some bioethanol-producing microorganisms like *P. stipitis* are not affected by furfural in low concentrations up to 0.5 g/L [193]. Moreover, it could have a positive effect on cell growth. Nigam [216] referred that ethanol yield and productivity were not affected by 0.27 g/L of furfural. However, concentrations above 1.5 g/L interfered in respiration and inhibited cell growth almost completely, and decreased ethanol yield by 90% and productivity by 85% [208].

Thus, the use of resistant microorganisms, such as engineered or adapted strains, would be preferable. In particular, laccase gene from *Trametes versicolor* was expressed into *S. cerevisiae,* which resulted higher ethanol productivity in spruce hydrolysates coniferyl aldehyde supplemented media [217].

8.2. Detoxification or removal of inhibitors

To improve the efficiency of hydrolysate fermentation, the inhibitors are required to be removed prior to fermentation [218]. The effectiveness of a detoxification method depends on the type of inhibitors present in the hydrolysate and the microorganisms to be used for the fermentation of the hydrolysate [219]. Several detoxification methods (physical, chemical and biological) have been used to convert inhibition compounds into inert materials or to reduce their concentration. Among the physical methods, evaporation removes volatile compounds such as acetic acid, furfural and vanillin [193]. Some chemical detoxification methods such as neutralization, calcium hydroxide overliming, use of ion exchange resins, activated charcoal or tin oxides [15,186]. Further, biological detoxification is substantially based on the enzymatic treatment using peroxidase and laccase obtained from the lignolytic fungus like *Trametes versicolor, Aspergillus nidulas* and *Trichoderma reseii*. The detoxified hemicellulosic sugars obtained through acid hydrolysis can be used efficiently for the production of ethanol by suitable fermentative microorganism [186].

9. Economic assessment

Lignocellulosic biomass has a complicated structure, which is more difficult to be converted into monomeric sugars compared to other sugary feedstocks such as starchy materials [220]. Additional cost is required in equipments and process operations since lignocelluloses are not meant to be readily accessible as a carbon source. The high capital and operation cost of pretreatment process has become a significant challenge to make the process viable. Apart from that, the enzymatic hydrolysis process to depolymerize the cellulose and hemicelluloses into fermentable sugars would be a considerable cost component [121].

Other features such as production/regeneration cost of catalyst, generation of higher-value lignin co-products and obtaining hemicellulose sugars in the liquid phase to reduce the need for pretreatment by using of hemicellulases forms the basis of comparison of different pretreatment options [117]. All these features are considered in order to pretreatment, results against their cost impact on downstream processing steps and the tradeoff with operational cost and capital cost [221]. However, as an integrated part of an industrial system or biorefinery, mass balance analysis can be used to validate the pretreatment efficacy of a process with any given feedstock [222].

Many investigators have attempted to estimate the cost of cellulosic ethanol, produced through different conversion technologies. Sassner et al. [223] have analyzed the cost effectiveness of three cellulosic feedstocks (namely salix, corn stover, and spruce) and concluded that conversion technology used for ethanol production has more important implications for the cost effectiveness of a conversion process than the type of feedstock used. Similarly, Hamelinck et al. [224] have concluded to minimize the production cost of ethanol produced using corn stover as a feedstock and co-current dilute acid prehydrolysis and enzymatic hydrolysis as a technology; emphasis should be given to increase the conversion efficiencies of hemicelluloses and cellulose to fermentable sugars. According to Bohlmann [225], feedstock costs have been found to be significant in determining the final cost of the ethanol, especially, when the conversion technology costs are falling at a faster pace. However, Huang et al. [226] have stated that the ethanol production cost using simultaneous saccharification and co-fermentation technology decreases with increasing plant sizes in the range of 1000 dry mg/day to 4000 dry mg/day.

10. Conclusions

Chemical pretreatment could prove to be an ideally suitable process for conversion of lignocellulosic biomass, including agricultural and forestry residues to sugars, and further processing for biofuels and other industrially important bioproducts. The conditions employed in the chosen pretreatment are one of the important parameters, which, in turn, govern the subsequent release of sugars by enzymatic saccharification. In addition, diverse advantages have also been reported for most of the pretreatment methods, which make them interesting for industrial applications.

Although, pretreatment systems and the concomitant release of bioproducts from lignocellulosic wastes have been greatly improved by new technologies, there are still challenges that need to be further investigated. These challenges include development of more efficient pretreatment and production technologies, bioprospecting and development of stable genetically engineered microorganisms, improved gene cloning and sequencing technologies and enhancement of production based on economies of scale for more efficient and cost effective conversions to value-added products. Further, in spite of removal of fermentation inhibitors,

the use of such resistant, adapted or engineered strains would be an added advantage for the fermentation.

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